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On January 31, 2002

TOWNSEND and TOWNSEND and CREW LLP

By: Joy M. Mansfield

PATENT
Attorney Docket No.: 021199-000100US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Pollack, William

Application No.: 09/660,862

Filed: September 13, 2000

For: METHOD OF MANUFACTURING IMMUNE GLOBULIN

Examiner: V. Ford

Art Unit: 1645

DECLARATION UNDER 37 C.F.R. § 1.132 OF DR. WILLIAM POLLACK

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, William Pollack, Ph.D., being duly warned that willful false statements and the like are punishable by fine or imprisonment or both (18 U.S.C. § 1001), and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

EXHIBIT A

1. All statements herein made of my own knowledge are true, and statements made on information or belief are believed to be true and correct.

2. I am currently chairman and chief executive officer of Atopix Pharmaceuticals Corporation, the assignee of the subject application.

3. I, Dr. Pollack, graduated from the Imperial College of Science and Technology at London University with a B.Sc degree in physiology and biochemistry. I received a M.Sc degree in chemistry and physics from the St. Georges Hospital Medical School at London University and a Ph.D. in immunology and immunochemistry from Rutgers University. A copy of my curriculum vitae is attached hereto as Exhibit A.

4. I am the named and true inventor of the above-referenced patent application. I have read and am familiar with the contents of the patent application. In addition, I have read the final Office Action, dated November 2, 2001, received in the present case. It is my understanding that the Examiner believes that the Zolton *et al.* patent, U.S. Patent Number 4,597,966, anticipates the manufacturing method of the present invention. It is also my understanding that the Examiner believes that Zolton *et al.* in combination with either Cheung *et al., Annals of Allergy*, Volume 50, March 1983, 155-160, Sirna, U.S. Patent No. 5,908,827, or Thomas, U.S. Patent No. 4,089,944 makes the invention of the present application obvious.

5. With this application, I claim a method of manufacturing a highly purified IgG4 immune globulin preparation. The method comprises the steps f adjusting

plasma to a pH of about 6.5 and a conductivity of between 3.5-6 millisiemens, and contacting the plasma with an anion exchange resin followed by a cation exchange resin to obtain a final effluent that comprises IgG4 essentially free of other IgG subtypes.

6. The Zolton method, unlike the method of the present application, does not result in an immunoglobulin preparation comprising IgG4 that is essentially free of other IgG subtypes. Zolton's method, instead, results in a purified stable IgG gamma globulin preparation containing all IgG subtypes including IgG1, IgG2, IgG3, and IgG4. In contrast, the present application provides a method of producing a purified IgG4 preparation free from IgG1, IgG2 and IgG3. Zolton's patent teaches a stabilized preparation of IgG (including all subtypes). The present application teaches a method of fractionating IgG into its various subtypes. It is neither suggested nor taught in the Zolton patent that the Zolton purification method results in pure IgG4 (free of all other subtypes), nor, in my opinion, could the purification system described in Zolton result in pure IgG4 free of other IgG subtypes.

7. Zolton's purification method utilizes a QAE-Sephadex anionic resin. In contrast, the present invention uses two resins, an anion exchange resin, e.g., DEAE Sepharose, followed by a cation exchange resin, e.g., CM-Sepharose. The extra fractionation step results in an IgG4 preparation free of other subtypes. Prior to the advent of the present invention, further fractionation of an IgG preparation into a purified IgG4 using chromatographic resins was not known. Again, the present invention provides a facile method of manufacturing IgG4 immune globulin that is essentially free of other IgG subtypes.

8. The purified IgG4 preparation has numerous advantages over an IgG preparation containing all of the IgG subtypes. The purer IgG4 preparation contains less protein and has a higher amount of blocking antibody per unit weight or per unit of protein that is being injected. The intravenous injection of many immune globulin products can lead to reactions that are caused by aggregation and fragmentation of the

immune globulin. The lower protein and higher blocking antibody content of the IgG4 preparation results in a preparation that is safer and more effective than the other less pure IgG preparations that contain IgG1, IgG2 and IgG3 as well as IgG4.

9. Further, the Zolton patent in view of Cheung *et al.*, or Sirna, or Thomas does not make obvious the manufacturing method of the present application, as the secondary references of Cheung *et al.*, Sirna, and Thomas do not address the deficiencies in the Zolton patent.

10. Cheung *et al.* documents a correlation between high IgG4 levels and beekeepers. This correlation, at most, indicates that there may be a role for IgG4 in the protection against anaphylactic reactions. Cheung *et al.* does not teach or suggest how to make a purified IgG4 preparation or even that a purified IgG4 preparation would be more desirable than a IgG preparation containing all of the IgG subtypes including IgG4.

11. Sirna teaches the use of ion exchange chromatography and high-resolution chromatography to extract purified polypeptide from human urine. I would not expect a purification system for the extraction of polypeptide from *human urine* to be relevant for the purification of *blood plasma* and immunoglobulins. Furthermore, the Sirna method utilizes multiple resins along with DEAE Sepharose and CM-Sepharose. Sirna does not teach or suggest the use of DEAE Sepharose and CM-Sepharose for the purification of IgG4 from human plasma.

12. Thomas teaches how to rapidly solubilize an anti-hemophilic factor composition. The Thomas reference does not teach or suggest how to make a purified IgG4 preparation. Furthermore, Thomas does not teach or suggest fractionation of IgG into an IgG4 fraction.

13. In view of the foregoing, it is my scientific opinion that, after reading the above mentioned references, the presently claimed method is novel and

unobvious over the cited art. One of skill in the art would not be motivated to make the purified IgG4 preparations using the method of the present application. Therefore, Zolton *et al.* does not anticipate this invention and Zolton *et al.* either alone or in combination with either Cheung *et al.*, Sirna, or Thomas does not make the invention of the present application obvious.

The declarant has further nothing to say.

Date: 1/28/02 By: William Pollack
William Pollack, Ph.D.

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